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| APPLICATION NO.                                                     | FILING DATE   | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO.  | CONFIRMATION NO. |
|---------------------------------------------------------------------|---------------|----------------------|----------------------|------------------|
| 10/554,122                                                          | 09/11/2006    | Brenda M. Ogle       | 07039-463US1         | 4639             |
| 26191                                                               | 7590          | 10/13/2009           | EXAMINER             |                  |
| FISH & RICHARDSON P.C.<br>PO BOX 1022<br>MINNEAPOLIS, MN 55440-1022 |               |                      | STRZELECKA, TERESA E |                  |
| ART UNIT                                                            | PAPER NUMBER  |                      |                      |                  |
|                                                                     | 1637          |                      |                      |                  |
| NOTIFICATION DATE                                                   | DELIVERY MODE |                      |                      |                  |
| 10/13/2009                                                          | ELECTRONIC    |                      |                      |                  |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

[PATDOCTC@fr.com](mailto:PATDOCTC@fr.com)

|                              |                        |                     |  |
|------------------------------|------------------------|---------------------|--|
| <b>Office Action Summary</b> | <b>Application No.</b> | <b>Applicant(s)</b> |  |
|                              | 10/554,122             | OGLE ET AL.         |  |
|                              | <b>Examiner</b>        | <b>Art Unit</b>     |  |
|                              | TERESA E. STRZELECKA   | 1637                |  |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 23 July 2009.  
 2a) This action is **FINAL**.                    2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 1-10, 13-17, 51 and 52 is/are pending in the application.  
 4a) Of the above claim(s) 9, 10, 16 and 17 is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 1-8, 13-15, 51 and 52 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
     Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
     Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

|                                                                                      |                                                                   |
|--------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ .                                    |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____.                                                         | 6) <input type="checkbox"/> Other: _____ .                        |

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's submission filed on July 23, 2009 has been entered.

2. Claims 1-10 and 13-17 were previously pending, with claims 9, 10, 16 and 17 withdrawn from consideration. Applicants amended claims 1, 2, 7, 9, 10, 14, 15 and 17, and added new claims 51 and 52. Claims 1-8, 13-15, 51 and 52 will be examined.

3. Applicants' amendments overcame all of the previously presented rejections. This office action contains new grounds for rejection necessitated by amendment.

### ***Priority***

4. The provisional application 60/464,981 (filed April 24, 2003) does not provide support for random nucleic acid molecules.

Therefore, the priority date of the instant claims is April 24, 2003.

### ***Claim Interpretation***

5. Applicants did not define the term "frequency of hybridization", therefore it is interpreted as any measure of hybridization, for example, a number of hybridized probes.

### ***Claim Rejections - 35 USC § 103***

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the

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subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

7. Claims 1-3, 6, 7, 13-15, 51 and 52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gehrman et al. (WO 03/044225; filed November 15, 2002; published May 30, 2003), Cho et al. (Appl. Env. Microbiol., vol. 68, pp. 1425-1430, March 2002) and Wagner et al. (PNAS USA, vol. 95, pp. 14447-14452, 1998; cited in the IDS).

A) Regarding claim 1, Gehrman et al. teach a method of determining lymphocyte diversity in a subject, the method comprising:

a) providing:

i) labeled nucleic acid molecules from a population of said subject's lymphocytes, wherein each of said labeled nucleic acid molecule encodes a lymphocyte receptor or a portion thereof (page 9, lines 24-30; page 11, lines 17-31; page 12; page 13, lines 1-9; page 19, lines 7-10),

ii) a population of nucleic acid molecules, wherein said population of nucleic acid molecules comprises random nucleic acid molecules or unselected express sequence tags (page 13, lines 11-19);

b) hybridizing said labeled nucleic acid molecules or fragments of said labeled nucleic acid molecules with said population nucleic acid molecules (page 13, lines 11-19; page 17, lines 1-5; page 19, lines 12-14);

c) assessing hybridization of said labeled RNA nucleic acid molecules with said population of nucleic acid molecules to determine the frequency of hybridization (page 13, lines 24-29; page 29, lines 17-20), and

d) quantifying the amount lymphocyte diversity in said subject (page 13, lines 24-29; page 14, lines 29-30; page 15, lines 1-2).

Regarding claims 2 and 3, Gehrmann et al. teach nucleic acid molecules attached to a solid substrate such as glass, silicon or nitrocellulose (page 13, lines 11-15; page 17, lines 7-10; page 19, lines 4, 5).

Regarding claim 6, Gehrmann et al. teach an array comprising different regions to which different nucleic acid molecules are attached (page 13, lines 11-15).

Regarding claim 7, Gehrmann et al. teach labeling of nucleic acids with fluorochromes (page 20, lines 1-3).

Regarding claims 13-15, Gehrmann et al. teach T lymphocytes, T cell receptors and CDR3 sequences (page 10, lines 23-26; page 11, lines 29-31; page 12, lines 8-11; page 16, lines 10-14; page 18, lines 16-18).

Regarding claims 51 and 52, Gehrmann et al. teach labeled RNA and DNA molecules (page 11, lines 17-31; page 12; page 13, lines 1-9; page 26, lines 1-2).

B) Gehrmann et al. teach quantification of the immune genes, but do not teach using a frequency of hybridization determined from a standard curve generated by hybridization of samples containing a known number of nucleic acid molecules.

C) Cho et al. teach determining a number of expressed genes from array hybridization using standard curves obtained by hybridizing samples with known numbers of gene copies to an array of oligonucleotides, and creating a standard curve based on the measurements (page 1425, second paragraph; Fig. 1, 2; page 1426, last paragraph; page 1427; Fig. 3).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the quantitation method for a number of gene sequences of Cho et al. in the method of determining lymphocyte diversity Gehrmann et al. The motivation to do so is provided by Gehrmann et al., who state that (page 4, lines 26-29; page 5, lines 1-6):

"The characterization of T cell responses in normal physiological and pathological situations, including auto-immunity, response to infectious agents, alloimmunity, and tumor immunity, is a key to understand disease control by the immune system and is beginning to play an important role in many clinical situations.

The totality of BCRs and TCRs being expressed by a vertebrate at a certain point in time, i.e., the vertebrates immune gene repertoire, mirrors the vertebrate's immune status. Hence, from a concise analysis of vertebrate's immune gene repertoire, one can draw conclusions on the immune status and on the susceptibility to diseases. In addition, ongoing diseases and inflammatory reactions can be assessed via the immune gene repertoire, and decisions for treatment may be concluded."

The expectation of success for quantitation of T cell repertoire is provided by Wagner et al., who examined TCR chain diversity in patients with rheumatoid arthritis and chronic infections (Abstract). Wagner et al. stated the following (page 14447, third paragraph):

"To estimate the diversity of the CD4 T cell repertoire, the frequency of individual TCR  $\beta$ -chains used by circulating CD4 T cells was determined, and the diversity of the TCR repertoire in healthy donors and RA patients was compared. RA patients differed from controls in that the majority of TCR  $\beta$ -chains were present at increased frequencies and that infrequent TCR  $\beta$ -chains were the exception. Restricted diversity of TCR  $\beta$ -chains was associated with an increased number of peripheral CD4 T cells undergoing proliferation and a loss of telomere length in the CD4 T cell compartment. In contrast to the findings in RA, chronic T cell responses to viral antigens in hepatitis C-infected patients did not shift the distribution of TCR  $\beta$ -chains. These data suggest that the entire TCR repertoire is altered in RA with a loss of diversity and multiclonal growth of a high proportion of T cells."

They concluded with the following (page 14452, last paragraph):

"Regardless of the precise mechanism for the loss of T cell diversity, these aberrations have important implications for the disease process and the way it is treated and studied. The fact that large proportions of the TCR repertoire are altered cannot remain without consequences for immunoresponsiveness. It is possible that the repertoire contraction will generate holes in the repertoire and therefore will lead to defective immune responses to selected antigens. The design of therapeutic approaches should consider that the RA repertoire already has lost diversity. So far, it has been assumed that it would be beneficial to deplete T cells. If these patients have difficulties repopulating the T cell compartment and have to generate new T cells through self-replication, T cell-directed therapies will compromise further their ability to maintain diversity. It is, therefore, not surprising that treatment trials using T cell depletion were not successful and had substantial side effects (31, 41). Very different therapeutic approaches will have to be taken to correct repertoire aberrations in an attempt to control the disease process and its complications."

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention that as precise as possible determination of lymphocyte diversity enables effective diagnosis and treatment of infections and immune diseases.

8. Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gehrmann et al. (WO 03/044225; filed November 15, 2002; published May 30, 2003), Cho et al. (Appl. Env. Microbiol., vol. 68, pp. 1425-1430, March 2002) and Wagner et al. (PNAS USA, vol. 95, pp. 14447-14452, 1998; cited in the IDS), as applied to claims 1 and 2 above, and further in view of Fulton et al. (Clin. Chem., vol. 43, pp. 1749-1756, 1997; cited in the previous office action).

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A) The teachings of Gehrmann et al., Cho et al. and Wagner et al. are presented above.

Gehrmann et al. teach solid support being a glass plate or chip, but do not teach beads or flow cytometry.

B) Fulton et al. teach multiplexing of analyte detection reaction using flow cytometry with fluorescently-labeled beads (Abstract; page 1749, second paragraph).

Regarding claim 4, Fulton et al. teach oligonucleotide probes immobilized on microspheres (page 1751, third seventh paragraph).

Regarding claim 5, Fulton et al. teach detection of nucleic acid hybridization by flow cytometry (page 1752, third paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used probes immobilized on beads and flow cytometry of Fulton et al. in the detection of lymphocyte diversity of Gehrmann et al., Cho et al. and Wagner et al. The motivation to do is provided by Fulton et al. (page 1755, second and last paragraphs):

“These studies have demonstrated the ability of the FlowMetrix system to perform highly multiplexed assays for analysis of specific protein–protein interactions, such as immunoassays, and for analysis of specific DNA sequences. The system provides several advantages for analysis of biologically and medically relevant molecules, including speed, economy, and advanced analytical capabilities. The system reduces assay time by performing multiple analyses simultaneously rather than sequentially. The no-wash format of many microsphere-based assays, particularly in the final detection step, is considerably faster than microtiter-based assays that require multiple washing steps to remove excess reagents. In addition, the rapid kinetics of microsphere-based assays allow shorter incubation times than conventional solid phase assays. The reduced assay time also reduces labor costs for performing multiple analyses. Reagent usage for microsphere-based assays is 10- to

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1000-fold less than microtiter-based assays. Multiplexing allows unique analysis of molecular interactions that can only be performed in a multiplexed format. “

The FlowMetrix system represents a revolutionary new technology that can be applied to virtually any application that requires analysis of molecular interactions, including basic research, clinical diagnostic testing, hightthroughput drug screening, environmental testing, and agricultural testing. This system is unique in its ability to provide multiplexed, high-throughput analysis coupled with real-time data analysis. The system offers excellent sensitivity, precision, speed, and economy.”

9. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gehrmann et al. (WO 03/044225; filed November 15, 2002; published May 30, 2003), Cho et al. (Appl. Env. Microbiol., vol. 68, pp. 1425-1430, March 2002) and Wagner et al. (PNAS USA, vol. 95, pp. 14447-14452, 1998; cited in the IDS), as applied to claims 1 and 7 above, and further in view of Allen et al. (U.S. Patent No. 6,017,710 A; cited in the previous office action).

A) Gehrmann et al. teach fluorescent labels in general (page 20, lines 1-3), and Cho et al. teach Cy3 and Cy5 labels (page 1427, first paragraph), but do not teach any of the labels listed in claim 8.

B) Allen et al. teach multiple fluorescent labels, including FITC, phycoerythrin or allophycocyanin (col. 14, lines 3-11).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used alternative fluorescent labels of Allen et al. in the method of Gehrmann et al., Co et al. and Wagner et al., since they are functionally equivalent compounds. As stated in MPEP 2144.06:

**2144.06 Art Recognized Equivalence for the Same Purpose**

**>II. < SUBSTITUTING EQUIVALENTS KNOWN FOR THE SAME PURPOSE**

In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. *In re Ruff*, 256 F.2d 590, 118 USPQ 340 (CCPA 1958) (The mere fact that components are claimed as members of a Markush group cannot be relied upon to establish the equivalency of these components. However, an applicant's expressed recognition of an art-recognized or obvious equivalent may be used to refute an argument that such equivalency does not exist.); \*\* *Smith v. Hayashi*, 209 USPQ 754 (Bd. of Pat. Inter. 1980) (The mere fact that phthalocyanine and selenium function as equivalent photoconductors in the claimed environment was not sufficient to establish that one would have been obvious over the other. However, there was evidence that both phthalocyanine and selenium were known photoconductors in the art of electrophotography. "This, in our view, presents strong evidence of obviousness in substituting one for the other in an electrophotographic environment as a photoconductor." 209 USPQ at 759.).

An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. *In re Fout*, 675 F.2d 297, 213 USPQ 532 (CCPA 1982).

10. No claims are allowed.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka  
Primary Examiner  
Art Unit 1637

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Primary Examiner, Art Unit 1637  
October 2, 2009